AMENDMENTS TO THE DRAWINGS:

The drawing figures have been amended to not refer to the same figure number.

REMARKS

The Examiner is thanked for the due consideration given the application. A substitute set of drawing figures has been provided. The specification has been amended to better refer to the drawing figures.

Upon entry of this amendment, claims 28, 30-34 and 37-61 are pending in the application. Claims 42, 43, 45 and 47-60 have been withdrawn. Claims 29, 35 and 36 have been canceled and their subject matter has been generally incorporated into independent claim 28. Claims 30-34 and 37 have been amended to not depend on a canceled claim.

No new matter is believed to be added to the application by this amendment.

Entry of this amendment under 37 CFR §1.116 is respectfully requested because it cancels claims, complies with a matter of form set forth in the Office Action, and places the application in condition for allowance.

Also, it is respectfully noted that the Office Action of September 17, 2008 (to which this paper responds) was the first action on the merits in which claims were rejected for statutory reasons. As a result, there has been no opportunity for a clear issue to develop between the applicant and the Office. See MPEP 706.07(b) for the criteria for a holding of finality on the first action.

Accordingly, the holding of finality should be withdrawn and the status of the application should properly be under non-final rejection.

The Drawings

The drawing figures have been objected to as being referred to by the same figure number. A substitute set of drawing has been filed concurrent with this paper in which the drawing figures have different figure numbers.

Rejection Under 356 USC §112, Second Paragraph

Claims 28-41, 44, 46 and 61 have been rejected under 35 USC §112, second paragraph as being indefinite. This rejection is respectfully traversed.

The Office Action asserts that the claims omit essential steps such as the steps for conducting an in vitro clonal test, the steps for testing the effect that different degrees of local collocation of cells has on the effect of the agent, and the steps for an in vivo test of clonal growth of immune cells. The comments in the Office Action have been considered, and these steps are now set forth in detail in independent claim 28.

The Office Action also points out issues of antecedent basis. The amended claim set has full antecedent basis.

The Office Action further asserts that the terms "liberation of the cells" and "potential toxin" as being

indefinite since the specification does not teach what the terms encompass.

The liberation of the cells is when cells are liberated from the tumour and will initiate local infiltration or a metastasizing process elsewhere in the body. This has been described in several experiments (experiments 4,9,14,18,23,25 and 26) in the specification and this term is a common expression for this process and obvious for one skilled in the art.

Potential toxins is a common expression to a toxin which are not toxic in healthy peoples, but unusual high concentrations, a special constitution, metabolism or disease may make intake of such potential toxins toxic. Intake of such compounds may occur through food, health food, drugs, air, water, cosmetics, and pollutions or by direct contact.

As a result, the claims are clear, definite and have full antecedent basis.

This rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

Rejection Under 356 USC §112, First Paragraph

Claims 28-41, 44 and 46 have been rejected under 35 USC §112, first paragraph as failing to comply with the written description requirement. This rejection is respectfully traversed.

The Office Action asserts that the method for testing and selecting an agent to determine whether the agent inhibits of

stimulates clonal growth comprising steps a) through d) are not supported in the specification as filed. This issue was addressed in the Amendment filed January 22, 2008.

However, the remarks filed January 22, 2008 were found not to be persuasive, and the Office Action asserts that since the specification did not support the method comprising the combination of the steps in claim 28, including step d).

First, step d) has been amended to be simplified to remove the term "of the subject."

Also, an objective standard for determining compliance with the written description requirement is: "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co.*, Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed.

Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)).

The claimed method is a three phase test (page 4 lines 23 – 25, page 42 line 9 and page 38 - 42 line 22), comprising a clonal test (page 38) followed by collocation inhibition test (page 40) and finally a test for influencing the development of metastasis (page 41) where the assay detecting the effect on clonal inhibition performed either in cell culture, in mice or in another animal is included. This disclosure reasonably conveys that the inventor has possession of the invention when the application was filed.

Further, possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

In this case, the specification has extensive experimental results demonstrating possession of the invention, as is evidenced, e.g., by the 65 pages of drawing figures.

As a result, the present invention is fully supported by the specification as filed.

This rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

Rejections Based on PRECHEL et al.

Claims 28-32, 34-36, 38-41, 44, 46 and 61 have been rejected under 35 USC §102(b) as being anticipated by PRECHEL et al. (*Cancer Letters*, 1995, 92: 235-242) as evidenced by CAR et al. (*Toxicologic Pathology*, 1999, Vol. 24: 58-63). Claim 33 has been rejected under 35 USC §103(a) as being unpatentable over PRECHEL et al. in view of DE ASUA et al. (*Proc. Natl. Acad. Sci. USA*, 1973, 70: 1388-1392) and KAMEI (*Cell Biol. Int. Rep.*, Jan 1987, 11(1): 35-41). Claim 37 has been rejected under 35 USC §103(a) as being unpatentable over PRECHEL et al. in view of TAMI et al. (U.S. Patent 4,744,985).

These rejections are respectfully traversed.

PRECHEL et al. evaluated the effects of IL-12 on immune parameters and tumor progression in an animal tumor model in which tumor production of GM-CSF leads to myelopoietic stimulation giving rise to an increased number of immune suppressive GM- progenitor cells that suppress anti-tumor immune responses. IL-12 augmented the myelopoietic stimulation that is

induced by the progressively growing tumor, although it diminished the proliferative potential of the myeloid progenitor cells. The presence of GM-CSF-induced immune suppressor cells in the bone marrow, spleen and tumor was not reduced by IL-12. T cell functions in tumor bearers were suppressed and this generally was not overcome by IL-12 treatment. While IL-I2 enhanced tumor-specific cytolytic activity in the draining lymph nodes, there were no effects on the frequency of intratumoral $CD8^+$ T-cells, on the growth of s.c. tumors, or on the formation of metastases.

In PRECHEL et al., there is no effect of IL-12 on metastases, and the article does not describe a specific affection of clonal growth that is different for collocated and scattered identical cells.

In contrast, the immune modulating effect of the specific clonal inhibitors of the present invention is a side-effect that is not wanted in connection with treatment of tumors or viral infections and is probably significant only for primary immune reactions. The effect on virus production is also linked to the specific nature of the inhibition of clonal growth since the metabolism of collocated identical cells is not significantly affected. Only marginal effects may be present.

Therefore, PRECHEL et al. fail to consider specific clonal inhibitors or enhancers, and IL-12 has no effect on

formation of metastases. Therefore, this PRECHEL et al. includes no relevant counter-arguments against my patent application.

The Office Action refers to CAR et al. as evidence of IL-12 is a heterodimeric cytokine produced by several types of cells but also has toxic effects.

However, CAR et al. conclude that recombinant murine interleukin (IL) 12 (rmIL-12) exhibits antitumor, antiviral, and antimicrobial activities and can modify allergic inflammatory reactions in animals models. Recombinant human IL-12 (rhlL-12) is currently in clinical trials for treatment of cancer, asthma, and viral hepatitis.

The specific clonal inhibitors, however, do not have general anti-tumor, antiviral, antimicrobial activities. Treatment with specific clonal inhibitors is expected only to inhibit activity in identical cells that were sparsely seeded in cultures or sparsely distributed among other cells in the body. The article does not describe an activity of lL-12 and related substances that are confined to only scarcely distributed identical cells in cultures or animals.

Therefore, the conclusion must be the same for both PRECHEL et al. and CAR et al.

PRECHEL et al. thus fail to consider specific clonal inhibitors or enhancers and thus fails to anticipate a claimed embodiment of the present invention.

PRECHEL et al. also fail to be a basis for an assertion of *prima facie* unpatentability.

The Official Action acknowledged that PRECHEL et al. fail to teach using BHK21/c13 and BHK21/C13 cells transformed with polyoma virus. The Official Action turns to DE ASUA and KAMEI.

The DE ASUA et al. reference shows that BHK 21/13 fibroblasts grown in the presence of insulin show some characteristics of a transformed strain. The effect is shown both in agar and when grown on surface.

In the experiments described in the present invention, insulin induces growth of normal cells in soft agar medium. Then specific clonal inhibitors can inhibit these cells, but only when they were sparsely distributed in the culture. This is possible since insulin stimulates both collocated cells and sparsely seeded cells in culture.

Therefore, the conclusion must be the same as for PRECHEL et al. and CAR et al., and DE ASUA et al. fail to consider specific clonal inhibitors or enhancers and is not a relevant counter-argument against my patent application.

KAMEI focuses on a test that may show inhibition of anchorage independent growth of transformed cells that may be suppressed by chemicals as retinoic acid. Anchorage independent growth is a growth pattern that transformed cells may show when growing on a surface, also called criss-cross appearance.

There is a connection between this appearance and the ability that such transformed cell lines have when growing in soft agar: they can form colonies in an agar where the untransformed parent cell line is unable to form colonies.

Therefore, what this test does is performed to select compounds with the ability to revert temporarily or may be more permanently, the transformed phenotype.

Moreover, not all fetal bovine sera (FBS) supported the suppression of anchorage independent growth of retinoic acid, and insulin enhanced the anchorage independent growth in both types of sera even in the presence of retinoic acid.

Hiroia Kamei's article may have been a logical counter argument against the present invention if the content of claim 28 was only: "A method for testing and selecting an agent to determine whether said agent inhibits or stimulates clonal growth." But there is more:

Claim 28, b) "testing the effect those different degrees of local collocation of cells has on the effect of said agent on cloning." This is elaborated in claims 48-52.

The selection of agents by the test described in the specification is based on the specific inhibition or specific stimulation of clonal growth of cells either seeded sparsely in (agar) culture or transplanted as single cells sufficiently diluted and scattered in tissues. No such inhibition or stimulation of growth of single cells occurs if these cells are

locally congregated (collocated) either in culture or in the animal. It is important to be aware that other cells in the animal do not affect the degree of collocation of the transplanted identical cells and thus not the specific inhibition or stimulation of the transplanted cells. It is only the distance between the identical transplanted single cells that counts, not the number of other cells in the body of the animal in the same area.

Therefore, development of local infiltration or metastases as well as growth of clones resistant to ongoing treatment will be inhibited or come to a stop by the specific clonal inhibitors detected and selected by the test.

The conclusion is that Kamei's article does not consider specific clonal inhibitors or enhancers and is not relevant to the present invention.

Regarding TAMAI et al., the Abstract sets forth that substances having carcinostatic and immunostimulating activity, which are obtained from a culture or its supernatant fluid prepared by culturing bacteria belonging to the Fusobacterium genus. The substances are useful for the treatment of cancerous diseases in lower warm-blooded animals. This disclosure concerns such substances and a process for preparing the same and a carcinostatic agent containing the same.

Column 1, third paragraph of TAMAI et al. states: ". . . a specific component obtained from the supernatant fluid has a

carcinostatic activity in lower warm-blooded animals; that said component has substantially no effect of inhibiting the formation of a colony of cancer cells in a colony forming assay method, and has not a carcinostatic activity by killing the cancer cells."

That is, TAMAI et al. teaches that the formation of colonies is not inhibited by these substances in a colony forming assay. That is completely different from compounds selected by my method described in my patent application where the inhibition is specifically directed against clonal growth of scarcely distributed identical cells.

Table 2 of TOMAI et al. indicates that: all fractions from TF-100 to TF-150 had an immune-stimulating activity.

In contrast, the selected specific clonal inhibitors of the present invention do not stimulate immunity. The primary immune reaction is, on the other hand, expected to be significantly suppressed. Table 2 indicates that: all fractions from TF-100 to TF-150 inhibited Ehrlich solid tumor. This effect of TF-1 10 and TF-1 20 is not described.

It is thus noted that the best specific clonal inhibitor 4-OH-OPB stimulated growth of Ehrlich solid tumor. Therefore, these fractions have nothing in common with the inhibitor of the present invention and there is no reason to believe that the specific clonal stimulators detected by my method would inhibit Ehrlich solid tumors.

The effects of the extracts of Tamai et al. are not thus in accordance with the effects of specific clonal inhibitors or stimulators detected by the method of the present invention.

As a result, no combination of the secondary references with PRECHEL et al. is sufficient to alleged *prima facie* unpatentability. Even if this unpatentabilty could be alleged, it would by dissipated by the unexpected results shown in the Examples and the drawing figures.

These rejections are believed to be overcome, and withdrawal thereof is respectfully requested.

Conclusion

The objections and rejections are believed to have been overcome, obviated or rendered moot and no issues remain. The Examiner is accordingly respectfully requested to place the application in condition for allowance and to issue a Notice of Allowability.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any

overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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APPENDIX:

The Appendix includes the following item(s):

☐ - a terminal disclaimer

☐ - a 37 CFR 1.132 Declaration

☐ - a new or amended Abstract of the Disclosure

☒ - Replacement Sheets for the drawings

☐ - a Substitute Specification and a marked-up copy of the originally-filed specification

☐ - a verified English translation of foreign priority document